PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 20 June 2000 (20.06.00)	
International application No. PCT/US99/24442	**Applicant's or agent's file reference** REISS1APCT
International filing date (day/month/year) 19 October 1999 (19.10.99)	**Priority date** (day/month/year) 19 October 1998 (19.10.98)
Applicant REISS, Carol, Shoshkes et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

18 May 2000 (18.05.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Juan Cruz
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

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WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
A61K 39/00, 39/395

A1

(11) International Publication Number: WO 00/23102

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(22) International Filing Date: 19 October 1999 (19.10.99)

(30) Priority Data:
60/104,817 19 October 1998 (19.10.98) US

(71) Applicant *(for all designated States except US)*: NEW YORK UNIVERSITY [US/US]; 70 Washington Square South, New York, NY 10012 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: REISS, Carol, Shoshkes [US/US]; 100 Bleecker Street #3A, New York, NY 10012 (US). KOMATSU, Takashi [US/US]; 157–04 24th Avenue, Whitestone, NY 11357 (US).

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(81) Designated States: CA, IL, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: METHOD FOR REGULATING THE PERMEABILITY OF THE BLOOD BRAIN BARRIER

(57) Abstract

The present invention relates to a method for regulating the permeability of the blood brain barrier by administering a NOS–3 inhibitor to reduce the increased permeability of the blood brain barrier caused by a pathological condition or by administering a NOS–3 activator or nitric oxide donor to increase the permeability of the blood brain barrier. By increasing the permeability of the blood brain barrier, a therapeutic or diagnostic compound can be delivered across this barrier into the central nervous system.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/24442

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :A61K 39/00, 39/395
US CL :424/130.1, 184.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/130.1, 184.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST, BIOSIS, CAPLUS, EMBASE, MEDLINE, USPATFULL, LIFESCI, SCISEARCH
search terms: nitric oxide synthase, NO, blood brain barrier

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X - Y	MINAMI et al. Roles of Nitric Oxide and Prostaglandins in the Increased Permeabillity of the Blood-Brain Barrier Caused by Lipopolysaccharide. Environmental Toxicology and Pharmacology. January 1998 Vol. 5, No. 1, pages 35-41, see entire document.	1-5 ---- 6-15
X - Y	BARNA et al. Activation of Type III Nitric Oxide Synthase in Astrocytes Following a Neurotropic Viral Infection. Virology. 1996, Vol. 223, pages 331-343, see entire document.	1-6 ---- 7-15
Y	US, 5,604,198 A (PODUSLO ET AL) 18 February 1997 (18/02/97), see entire document.	7-15

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 DECEMBER 1999	10 FEB 2000

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	NANCY OGIHARA
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/24442

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,527,527 A (FRIDEN) 18 June 1996 (18/06/96), see entire document.	7-15
Y	US 5,670,477 A (PODUSLO et al) 23 September 1997 (23/09/97), see entire document.	7-15

PATENT COOPERATION TREATY

FEB 1 4 2001

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: ROGER L. BROWDY
BROWDY AND NEIMARK, P.L.L.C.
624 NINTH STREET N.W., SUITE 300
WASHINGTON, D.C. 20001

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing *(day/month/year)*	12 FEB 2001
Applicant's or agent's file reference REISS1APCT	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/US99/24442	19 OCTOBER 1999	19 OCTOBER 1998

Applicant
NEW YORK UNIVERSITY

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	ARDIN MARSCHEL Dorothea Laurence For
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

Form PCT/IPEA/416 (July 1992) ★

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference REISS1APCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/24442	International filing date *(day/month/year)* 19 OCTOBER 1999	Priority date *(day/month/year)* 19 OCTOBER 1998
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 39/00, 39/395 and US Cl.: 424/130.1, 184.1		
Applicant NEW YORK UNIVERSITY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18 MAY 2000	28 DECEMBER 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Dorothea Lawrence for ARDIN MARSCHEL Telephone No. (703) 308-0196

Form PCT/IPEA/409 (cover sheet) (July 1998) ★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/24442

I. Basis of the report

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-67 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the claims:
pages 68-70 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the drawings:
pages 1-24 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the sequence listing part of the description:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [ ] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/24442

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	4-15	YES
	Claims	1-3	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-15	NO
Industrial Applicability (IA)	Claims	1-15	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1-3 lack novelty under PCT Article 33(2) as being anticipated by Minami et al (Environmental Toxicology and Pharmacology, Vol. 5, pp. 35-41, January 1998).

Minami et al disclose a method of for regulating the permeability of the blood brain barrier (BBB) comprising administering to rats a composition comprising a nitric oxide synthase-3 (NOS-3) regulating agent. Minami et al administer lipopolysaccharide (LPS) through intraperitoneal injection which causes increased permeability to the blood brain barrier during bacterial infection (i.e. a pathological condition) (see page 36, left column, lines 8-10) by producing nitric oxide (NO) (see Methods and page 39, left column, line 8). Minami et al administer amino guanidine and the L-arginine analog L-NG-Nitro-L-arginine methyl ester (L-NAME) which is a non-isozyme-selective NOS inhibitor (see Abstract and Methods) 15 minutes (i.e. contemporaneously) and 1 hour after the LPS which effectively reduces the increased permeability of the blood brain barrier caused by treatment with (LPS) (see Figure 3). Minami et al therefore meet the limitations of the claims.

Claims 1-6 and 8 lack an inventive step under PCT Article 33(3) as being obvious over Minami et al (Environmental Toxicology and Pharmacology, vol. 5, pp. 35-41, January 1998) in view of Poduslo et al (U.S. Patent No. 5,670,477).

The teachings of Minami et al are set forth above. Minami et al do not teach of local administration of a composition comprising a NOS-3 regulating agent to regulate the permeability of the BBB.

Poduslo et al teach of methods of administering pharmaceutical compositions to increase the permeability of the BBB (see column 17, last paragraph). The methods include local administration comprised of inhalation (column 18, line 7) and injection into the brachial vein (see column 25, line 24) for the purpose of limiting diffusion and breakdown of the pharmaceutical (Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
compound before reaching its intended destination.

Given that 1) Minami et al disclose methods of administering NOS-3 regulating agents which reduce the increased permeability of the BBB caused by administration of LPS, and 2) that Puduslo et al teach of local administration of pharmaceutical compounds for the purpose of increasing the permeability of the BBB, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to administer the permeability regulating agents of Minami et al by inhalation or brachial artery injection in view of Poduslo et al teaching the benefits of limiting diffusion and breakdown of the pharmaceutical compound.

Claims 1, 4, 6, and 7, 9-15 lack an inventive step under PCT Article 33(3) as being obvious over Barna et al (Virology, Vol. 223, 331-343, 1996) in view of Friden et al (U.S. Patent Nol 5,527,527).

Barna et al teach of a method of for regulating the permeability of the blood brain barrier comprising administering to mice a composition comprising a nitric oxide synthase-3 (NOS-3) regulating agent. Barna et al intranasally (i.e. locally) administer vesicular stomatitis virus (VSV) to mice (see page 335, left column last 2 lines) which is disclosed to disrupt the blood brain barrier (BBB) caused by the increased levels of NO (see page 339, last 3 lines) (i.e. a NOS-3 activator). Barna et al also administer interleukin-12 (IL-12) to the VSV infected mice which increased levels of NO, as shown by the increased levels of the nitrite (NO2-), a stable end-product of NO (see page 332, left column, 1st full paragraph), thus effectively increasing the permeability of the BBB. Barna et al further teach that besides IL-12, IFN-gamma and TNF-alpha also activate NOS-3 to effectively increase the permeability of the BBB (see page 332, left column, 1st full paragraph) to mediate the broad range of effects of both innate and acquired immunity associated with infection (see page 335, right column, 2nd full paragraph).

Barna et al do not teach of a method of regulating the permeability of the blood brain barrier by administering a composition comprising both a NOS-3 activator (or NO donor) and a neurologically active therapeutic compound or diagnostic compound.

Friden et al teach of a method of administering across the blood brain barrier the OX-26 antibody (i.e. a diagnostic compound, a targeting molecule) conjugated to (i.e. associated with) a neuropharmaceutical or diagnostic agent, where the antibody binds to the transferrin receptor on brain capillary endothelial cells (see column 2, first paragraph). Friden et al further teach that neuropharmaceutical agents conjugated to the antibody include cytokines and lymphokines (see column 3, line 31).

Given that 1) Barna et al teach that upon administration of IL-12, NOS-3 is activated to produce NO which in turn increases the permeability of the BBB, and 2) that Friden et al teach of administering a conjugate formed by the OX-26 antibody and a neuropharmaceutical compound such as an interleukin for the purpose of administering a therapeutic across the BBB, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to administer the OX-26 antibody conjugated to an interleukin such as IL-12 so as to cross the BBB since Barna et al teach of the potential advantages of using IL-12 for its ability to enhance permeability of the blood brain barrier and its beneficial effects in the immune response. Although Friden et al teach that the OX-26 antibody is able to cross the BBB, one of skill in the art would have been motivated to utilize IL-12 to further increase the permeability of the BBB.

---------- NEW CITATIONS ----------
NONE